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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 07/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/454,481	ALLISON ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 April 2004 and 05 June 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-21,23-25,27,28 and 31* is/are pending in the application.

4a) Of the above claim(s) *13-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21,23-25,27,28 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ n Disclosure Statement(s) (PTO-1449 or PTO/SB/08) (s)/Mail Date *20040610*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 5, 2003 has been entered.

2. The amendment filed April 12, 2004 is acknowledged and has been entered. Claims 21 and 23-25 have been amended.

3. Claims 13-21, 23-25, 27, 28, and 31 are pending in the application. Claims 13-20 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention.

4. Claims 21, 23-25, 27, 28, and 31 are currently under prosecution.

Information Disclosure Statement

5. The information disclosure filed June 10, 2004 has been considered. An initialed copy is enclosed.

Grounds of Claim Rejections Withdrawn

6. Applicant's amendment to claim 21 has obviated the ground of rejection under 35 USC § 112, second paragraph, which was set forth in section 10(a) of the previous Office action, since the body of the present claim recites a process step positively correlating to the objective recited in the preamble. Furthermore, upon consideration in view of Applicant's remarks, the ground of rejection under 35 USC § 112, second paragraph, which was set forth in section 10(b) of the previous Office action has been

withdrawn, since the CTLA-4 blocking agent must bind specifically to the extracellular domain of CTLA-4 and thereby inhibit CTLA-4-mediated signaling. Otherwise, unless specifically reiterated below, the grounds of claim rejections set forth in the previous Office action mailed December 5, 2002 have been withdrawn in favor of the new grounds of rejection set forth herein.

Priority

7. Applicant's claim for domestic priority under 35 U.S.C. §§ 119(e) or 120 is acknowledged. However, both the provisional application and the non-provisional application upon which priority is claimed fail to provide adequate support under 35 U.S.C. 112 for claim 21 of this application. In particular, both US Provisional Application No. 60/110,761 and US Application No. 08/760,288 fail to provide support for a method for inhibiting the growth of "non-T cell tumor cells" in a mammalian host. Furthermore, US Application No. 08/760,288 fails to provide support for the method comprising contacting at least one T cell of said host with a "self antigen preparation comprising a tissue specific self antigen", wherein said contacting is effective to stimulate "an autoreactive T cell response". Accordingly, the effective filing date of the instant application is December 3, 1999.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 21, 23-25, 27, 28, and 31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a new matter rejection.

Claim 21 recites the term, "non-T cell tumor cells". However, it does not appear that the specification, including the claims, as originally filed, provides proper and sufficient written support for the term. The disclosure of the contra-indication at page 21 (lines 7-13), which suggests the subject blocking agents may not be used to treat certain lymphomas, is too inadequate to support the recitation of "non-T cell tumor cells" in the claims. Furthermore, there does not appear to be proper and sufficient written support in either application to which the instant application claims priority, namely US Provisional Application No. 60/110,761 and the originally filed US Application No. 08/760,288. Claim 21 was added by the amendment filed June 23, 2000; but Applicant did not identify particular disclosures set forth in the specification, including the claims, as originally filed, which Applicant believes provides the necessary written support for the language of claim 21. The recitation of "non-T cell tumor cells" therefore appears to introduce new matter and violates the written description requirement set forth under 35 USC § 112, first paragraph.

In addition, claim 21 recites, "wherein said self antigen is expressed on tissue cells and non T cell tumor cells *arising from said tissue*" (italicized for emphasis). At page 4 (paragraph 3) of the amendment filed June 5, 2003, Applicant has remarked that claim 21 has been amended consistent with the descriptions in the specification, for example on page 9, lines 15-19, and pages 11-13. Nevertheless, the specification does not appear to provide the necessary written support for the recitation that the non T cell tumor cells arise from a tissue commonly expressing a self antigen. At page 19, the specification discloses, "a self antigen common to both normal and cancerous tissue can be targeted"; however, this disclosure fails to provide the necessary written support for the claim language, since the disclosure does not specify that the cancerous tissue arises form the normal tissue, which commonly expresses the self antigen. Accordingly, reciting "wherein said self antigen is expressed on tissue cells and non T cell tumor cells arising from said tissue" in claim 21 appears to introduce new matter and thereby violates the written description requirement set forth under 35 USC § 112, first paragraph.

These issues might be resolved if Applicant were to point to particular disclosures in the specification, including the claims, as originally filed, which are believed to provide the necessary written support for the language of claim 21.

10. Claims 21, 23-25, 27, 28, and 31 are under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims without having to first perform an undue amount of additional experimentation for the reasons set forth in section 7 of the previous Office action. Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). These factors include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

At pages 5 and 6 of the amendment filed December 8, 2003, Applicant has traversed the ground of rejection of the claims under 35 USC § 112, first paragraph, as lacking an enabling disclosure, for set forth in the previous Office action. Applicant has cited Hodi et al. (Exhibit A) and Phan et al. (Exhibit B), asserting these references demonstrate the ability of anti-CTLA-4 antibodies directed against CTLA-4 extracellular domain and inhibitory of CTLA-4 signaling to inhibit the growth of tumor cells.

Applicant's arguments have been carefully considered but have not been found persuasive for the following reasons:

Sotomayer et al., Christadoss et al., Sullivan et al., Zhu et al., Chambers et al., Gribben et al., Anderson et al., and Yang et al., which were cited in the previous Office action, address the problems particularly associated with the use of a CTLA-4 blocking agent. Bodey et al., Ezzel, Spitler, Boon, Timmerman et al., Arceci, Lee et al., Zaks et al., Gao et al., all of record, address more general limitations of cancer vaccines or problems associated with the application of specific cancer vaccines. The teachings of the references provide a reasonable and sound scientific basis for rejection of the claims under 35 USC § 112, first paragraph. Hodi et al. and Phan et al. teach the blockade of CTLA-4 function by contacting T cells expressing CTLA-4 with an anti-CTLA-4 antibody inhibits the growth of moderately immunogenic tumors and, in combination with cancer vaccines, increases the rejection of poorly immunogenic tumors, albeit with loss of tolerance to normal differentiation antigens; see, e.g., the abstract of Hodi et al. However, Hodi et al. teaches that while the treatment of patients previously immunized with irradiated, autologous GMCSF-secreting tumor cells with anti-CTLA-4 antibody resulted in the reduction or stabilization of CA-125 levels in patients with ovarian cancer and tumor necrosis in patients with melanoma, the treatment of melanoma patients previously immunized with defined melanosomal antigens failed to elicit an immune response that resulted in tumor necrosis (abstract). Hodi et al. concludes the CTLA-4 antibody-mediated blockade increases tumor immunity in *some previously vaccinated* patients (abstract). Accordingly, Hodi et al. strengthens the Office's position that Applicant's disclosure would not provide sufficient guidance, direction, and exemplification to enable the skilled artisan to use the claimed invention without first having to perform an undue amount of additional experimentation, since Hodi et al. shows that the skilled artisan cannot predict whether the claimed invention can be used to successfully inhibit the growth of any non-T cell tumor cells in a mammalian host.

In addition, Phan et al. teaches that while 21% of the melanoma patients that participated in the study benefited from cancer regression, 43% of the patients developed autoimmune disease, including autoimmune enterocolitis and hepatitis (abstract). The incidence of autoimmunity in mammals treated according to the claimed

methods was referred to in previous Office actions as reason that the skilled artisan could not use the claimed invention without first having to perform an undue amount of additional experimentation to determine how this potentially deleterious side-effect of the treatment might be abrogated or minimized.

Furthermore, while the teachings of Hodi et al. and Phan et al. are limited to an application of an anti-CTLA-4 antibody-mediated blockade of CTLA-4 activity, the claims more broadly encompass the use of any CTLA-4 blocking agent capable of binding specifically to CTLA-4 and inhibiting CTLA-4 signaling, which necessarily comprises an antibody or a fragment thereof but which antibody or fragment does not necessarily bind CTLA-4 or inhibit its signaling. Notably, the specification fails to teach the skilled artisan to make at least a substantial number of the members of the genus of "CTLA-4 blocking agents" to which the claims are directed, since the specification merely provides adequate guidance and direction to enable the skilled artisan to produce an anti-CTLA-4 antibody capable of binding to the extracellular domain of CTLA-4 and inhibiting its signaling.

Finally, noting that the claims are drawn to a process effective to break immune tolerance against a self antigen expressed by tumor cells and also by the normal tissue cells from which the tumor cells arose, such that the process stimulates an autoreactive T cell response against both the tumor cells and the normal cells, Frauwirth et al. (*J. Immunol.* **164**: 2987-2993, 2000) teaches T cell anergy can be induced in the absence of CTLA-4 signaling; see, e.g., the abstract. Accordingly, although the "CTLA-4 blocking agent" may be effective to block CTLA-4 signaling, it would not be expected that the agent can be effective to break immune tolerance, because Frauwirth et al. teaches T cell anergy, i.e., immune tolerance, can be induced independently of CTLA-4 signaling. It therefore again noted that the previous Office action cited Sotomayor et al. as teaching that, while CTLA-4 blockade can enhance priming of responsive T cells, it does not prevent the induction of tolerance to tumor antigens; see, e.g., the abstract.

11. Claims 21, 23-25, 27, 28, and 31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in

such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons set forth in section 8 of the previous Office action.

At page 4 of the amendment filed June 5, 2003, Applicant has traversed this ground of rejection, remarking the amendments to the claims are consistent with the disclosure in the specification and resolve any issues of written description.

Applicant's remarks have been carefully considered but have not been found persuasive for the following reasons:

Claim 21 presently recites, "wherein said CTLA-4 blocking agent *comprises* an antibody or a fragment thereof" (italicized for emphasis). The CTLA-4 blocking agent is not limited to an antibody, nor is it limited to an antigen-binding fragment thereof. Moreover, the CTLA-4 blocking agent does not necessarily comprise an antibody or a fragment thereof, which antibody or fragment is capable of binding specifically to the extracellular domain of CTLA-4 and inhibiting CTLA-4 signaling. Accordingly, although the members of the genus of "CTLA-4 blocking agents" commonly comprise an antibody or a fragment of an antibody the claim encompasses a genus of "CTLA-4 blocking agents", the members of the genus can vary markedly in structure. For example, the claim encompasses a non-antibody ligand of CTLA-4, which is fused or conjugated to an immunoglobulin effector domain. For the reasons set forth previously, Applicant's disclosure of the invention would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention, since the skilled artisan could not immediately visualize, recognize, or distinguish at least a substantial number of the members of the genus of "CTLA-4 blocking agents" capable of binding CTLA-4 and inhibiting its signaling activity.

In deciding *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the Court held that a generic statement that defines a genus of nucleic acids *by only their functional activity* does not provide an adequate written description of the genus. By analogy, a generic statement that defines the members of the genus of

"CTLA-4 blocking agents" to which the claims are directed *by only a common functional activity* does not adequately describe the whole of the genus. The Court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a precise definition of a representative number of members of the genus, such as by reciting the structure, formula, chemical name, or physical properties of those members, rather than by merely reciting a wish for, or even a plan for obtaining a genus of molecules having a particular functional property. The recitation of a functional property alone, which must be shared by the members of the genus, is merely descriptive of what the members of genus must be capable of doing, not of the substance and structure of the members.

MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description" Requirement (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show

that the applicant was in possession of the claimed invention" (*Id.* at 1104). The *Guidelines* further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. Because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant were in possession of the claimed invention at the time the application was filed.

12. Claims 21, 23-25, 27, 28, and 31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In addition to those reasons set forth in the above rejection, claims 21, 23-25, 27, 28, and 31 are rejected under 35 USC § 112, first paragraph, as lacking an adequate written description, because claim 21 is directed to the use of a self antigen preparation comprising a member of a genus of "tissue specific" self antigens. At page 20, lines 1-7, the specification describes some "tissue specific" self antigens. However, none of the exemplified self antigens are actually tissue specific, since, for example, Her2/neu (ErbB2) is not actually mammary-specific because it is also expressed, for example, in prostatic tissue and PSA is not actually prostate specific because it is also expressed in

breast tumors and normal breast, colon, ovary, liver, kidney, adrenal, and parotid tumors; see Zhau et al. (*Mol. Carcinog.* **5**: 320-327, 1992; particularly the abstract). And Lavesque et al. (*J. Clin. Lab. Anal.* **9**: 123-128, 1995; particularly the abstract). Accordingly, the written description would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

14. Claims 21, 23, 27, and 31 are rejected under 35 U.S.C. § 102(b) as being anticipated by Leach et al. (*Science* **271**: 1734-1736, 1996; of record), as evidenced by van Elsas et al. (*J. Exp. Med.* **190**: 355-366, 1999; of record).

As evidenced by van Elsas et al., contacting T cells in a mammalian host with the anti-CTLA-4 antibody of Leach et al. is capable of breaking immune tolerance to stimulate an autoreactive T cell immune response to normal cells and tumor cells expressing a common self antigen; see entire document, particularly the paragraph bridging pages 361 and 362 and page 364, column 1.

Leach et al. teaches that which is set forth in the previous Office action. In addition, it is noted that Leach et al. teaches the tumor cells injected into the mice were transfected to express B7-1 (page 1 of 5 of the Internet published article, paragraph 3). B7-1 is an immune stimulating agent; and in fact, Leach et al. teaches B7-1 expression induces an immune response that causes partial tumor rejection of the transplantable murine colon carcinoma (page 1 of 5 of the Internet published article, paragraph 3). Accordingly, Leach et al. teaches a method for inhibiting the growth of non-T cell tumor cells in a mammalian host comprising contacting T cells in the host with (a) a self antigen preparation comprising a tissue specific self antigen expressed on tissue cells and non-T cell tumor cells arising from the tissue and an immune stimulating agent, i.e., B7-1, and (b) an anti-CTLA-4 antibody that binds the extracellular domain of CTLA-4 and inhibits its signaling.

At pages 5-8 of the amendment filed June 5, 2003, Applicant has traversed the ground of rejection under 35 USC § 102(a) set forth in the previous Office action, arguing that Leach et al. does not anticipate the claimed invention because the Office has failed to point to objective evidence in the prior art that the carcinoma cell lines express self antigen, which is commonly expressed on the tissue from which the tumor cells arose and that contacting T cells in the mammalian host was sufficient to break immune tolerance against such a self antigen. Furthermore, Applicant has contended that the Office has failed to point to any evidence that it was recognized by the prior art that the process of the prior art increased activation of autoreactive T cells against both tissue cells and non-T cell tumor cells.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

At page 19, lines 18-21, the specification discloses: "The self antigen preparation may comprise a mixture of antigens, such as tumor lysates or irradiated tumor cell vaccines, as well as purified antigen comprising a specific self antigen of interest (e.g., protein, carbohydrate and the like) or a mixture of self antigens". At page

19, line 12, the specification discloses a self antigen, which is common to both normal and cancerous tissue, can be targeted; but the specification does not teach the self antigen must be expressed by the tumor cells and the normal cells from which the tumor cells initially arose. Otherwise, the specification provides no guidance as to what does or does not constitute a suitable "self antigen preparation". The prior art teaches contacting T cells in the mammalian host with "a self antigen preparation" comprising tumor cells, which arose from a tissue of origin that commonly expresses a mixture of proteins, carbohydrates and the like. Accordingly, absent a showing of any difference, the "self antigen preparation" comprising the tumor cells of the prior art is deemed the same as the "self antigen preparation" of the claims.

Applicant has argued that the prior art fails to teach the process of the prior art is effective to break immune tolerance, thereby stimulating an autoreactive T cell response against normal tissue expressing a self antigen of which the "self antigen preparation" is comprised. The process of the prior art is effective to inhibit the growth of non-T cell tumor cells, which suggests the process of the prior art elicits an immune response against any one or a mixture of proteins, carbohydrates, and the like expressed by the tumor cells. As evidenced by van Elsas et al., contacting T cells in a mammalian host with the anti-CTLA-4 antibody of Leach et al. is capable of breaking immune tolerance to stimulate an autoreactive T cell immune response to normal cells and tumor cells expressing a common self antigen; see entire document, particularly the paragraph bridging pages 361 and 362. Therefore, the process of the prior art is deemed the same as the claimed process, absent a showing of any difference. The Office, hwoever, does not have the facilities to determine if the process of the prior art was effective because the process elicited an immune response directed against an antigen that is commonly expressed by the normal cells from which the tumor cells originated, as opposed to an immune response against a unique tumor antigen not commonly expressed by normal cells of the same tissue type. Accordingly, if the process of the prior art and the claimed process are different, the burden is upon the Applicant to prove that the claimed process is different than the process taught by the prior art. See *In re*

Best, 562 F.2d 1252, 195 USPQ 430 (CCPA, 1977) and *Ex parte Gray*, 10 USPQ2d 1922 1923 (PTO Board of Patent Appeals and Interferences, 1988 and 1989).

Responding to Applicant's contention that the Office has failed to point to any evidence that it was recognized by the prior art that the process of the prior art increased activation of autoreactive T cells against both tissue cells and non-T cell tumor cells, it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. Even though the claims are drawn to process that is effective to break immune tolerance against a self antigen and stimulate an autoreactive T cell immune response against normal tissue cells expressing the self antigen, the claimed methods do not appear to distinguish the prior art teaching the same methods to achieve the same end result, namely the inhibition of tumor growth. The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. See *In re Wiseman,* 201 USPQ 658 (CCPA 1979). Furthermore, granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. See *In re Baxter Travenol Labs,* 21 USPQ2d 1281 (Fed. Cir. 1991). See MPEP § 2145. The Court of Appeals for the Federal Circuit has stated that "[I]t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable" See *In re Woodruff*, 919 F.2d 1575, 1578, 16 USPQ2d 1575, 1936 (Fed. Cir. 1990) (emphasis in original). See also *Bristol-Myers Squibb Company v. Ben Venue Laboratories*, 58 USPQ2d 1508 (CAFC 2001) at 1514: "Newly discovered results of known processes directed to the same purpose are not patentable because such results are inherent". As to inherency, the Court has noted that "[u]nder the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claimed limitations, it anticipates." *Mehl/Biophile Int'l Corp. v. Miligraum*, 192 F.2d 1362, 1366, 52 USPQ2d 1303, 1305 (Fed. Cir. 1999) (citations omitted). Moreover, "[w]here [...] the result is necessary consequence of what was deliberately intended, it is no import that the

article's authors did not appreciate the results." *Mehl/Biophile Int'l Corp*, 192 F.2d 1362, 52 USPQ2d at 1307.

15. Claims 21, 23-25, 27, 28, and 31 are rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,811,097 A (of record), as evidenced by Lavesque et al. (*J. Clin. Lab. Anal.* **9**: 123-128, 1995) and van Elsas et al. (*J. Exp. Med.* **190**: 355-366, 1999; of record).

As evidenced by Lavesque et al., both prostate tumor cells and the normal prostate cells from which the tumor cells arose express PSA (abstract).

As evidenced by van Elsas et al., contacting T cells in a mammalian host with the anti-CTLA-4 antibody of Leach et al. is capable of breaking immune tolerance to stimulate an autoreactive T cell immune response to normal cells and tumor cells expressing a common self antigen; see entire document, particularly the paragraph bridging pages 361 and 362 and page 364, column 1.

U.S. Patent No. 5,811,097 A ('097) teaches that which is set forth in the previous Office action. In addition, '097 teaches that the T cells of the mammal can also be contacted with an immune stimulating agent, e.g., GM-CSF (see, e.g., column 8, lines 37-57).

At pages 8 and 9 of the amendment filed June 5, 2003, Applicant has traversed the ground of rejection under 35 USC § 102(e) set forth in the previous Office action, arguing that '097 does not anticipate the claimed invention because the present claims recite the use of a preparation containing self antigen expressed on tissues from which the non-T cell tumor cells arose to break immune tolerance against the self antigen and thereby elicit an autoreactive immune response against both the tumor cells and the normal tissue cells. Again, Applicant has contended that the Office has failed to point to

objective evidence in the prior art that tumor cell lysates necessarily contain a self antigen present on a tissue from which the tumor cells arose.

Applicant's arguments have been carefully considered but not found persuasive for the reasons set forth above in response to Applicant's arguments traversing the rejection of the claims over Leach et al. In addition, at column 9 (lines 42 and 43), '097 discloses that suitable tumor antigens include, for example, prostate specific antigen (PSA), which at page 20 (lines 3 and 4) the instant specification teaches is a tissue-specific self antigen. Furthermore, as evidenced by Lavesque et al., both prostate tumor cells and the normal prostate cells from which the tumor cells arose express PSA (abstract). Regarding Applicant's assertion that the prior art did not recognize that the process breaks immune tolerance, it is aptly noted that at columns 1 and 2, the patent discusses "anergy", which is the state of immune tolerance; and in the abstract, for example, the patent discloses: "When CTLA-4 signaling is thus blocked, the T cell response to antigen is released from inhibition". The release from inhibition to which the abstract refers would be understood by the artisan ordinarily skilled in the art to mean a break in immune tolerance or reversion from an anergic state.

16. Claims 21, 23-25, 27, 28, and 31 are rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5,855,887 A, as evidenced by Lavesque et al. (*J. Clin. Lab. Anal.* **9**: 123-128, 1995) and van Elsas et al. (*J. Exp. Med.* **190**: 355-366, 1999; of record).

As evidenced by Lavesque et al., both prostate tumor cells and the normal prostate cells from which the tumor cells arose express PSA (abstract).

As evidenced by van Elsas et al., contacting T cells in a mammalian host with the anti-CTLA-4 antibody of Leach et al. is capable of breaking immune tolerance to stimulate an autoreactive T cell immune response to normal cells and tumor cells

expressing a common self antigen; see entire document, particularly the paragraph bridging pages 361 and 362 and page 364, column 1.

U.S. Patent No. 5,855,887 A ('887) teaches that which is set forth in the previous Office action. In addition, '887 teaches that the T cells of the mammal can also be contacted with an immune stimulating agent, e.g., GM-CSF (see, e.g., column 8, lines 25-45).

Applicant has traversed this ground of rejection under 35 USC § 102(e), arguing that '887 does not anticipate the claimed invention for the same reasons that '097 does not.

Applicant's arguments have been carefully considered but not found persuasive for the reasons set forth above in response to the same arguments, which Applicant also used to traverse the rejection of the claims over '097. In addition, at column 9 (lines 27 and 28), '887 discloses that suitable tumor antigens include, for example, prostate specific antigen (PSA), which at page 20 (lines 3 and 4) the instant specification teaches is a tissue-specific self antigen. Furthermore, as evidenced by Lavesque et al., both prostate tumor cells and the normal prostate cells from which the tumor cells arose express PSA (abstract). Regarding Applicant's assertion that the prior art did not recognize that the process breaks immune tolerance, it is aptly noted that at columns 1 and 2, the patent discusses "anergy", which is the state of immune tolerance; and in the abstract, for example, the patent discloses: "When CTLA-4 signaling is thus blocked, the T cell response to antigen is released from inhibition". The release from inhibition to which the abstract refers would be understood by the artisan ordinarily skilled in the art to mean a break in immune tolerance or reversion from an anergic state.

17. Claims 21, 23, 24, 27, and 31 are rejected under 35 U.S.C. § 102(b) as being anticipated by Hurwitz et al. (*Proc. Natl. Acad. Sci. USA* **95**: 10067-10071, 1998; of record) as evidenced by van Elsas et al. (*J. Exp. Med.* **190**: 355-366, 1999; of record).

As evidenced by van Elsas et al., contacting T cells in a mammalian host with the anti-CTLA-4 antibody of Leach et al. is capable of breaking immune tolerance to stimulate an autoreactive T cell immune response to normal cells and tumor cells expressing a common self antigen; see entire document, particularly the paragraph bridging pages 361 and 362 and page 364, column 1.

Hurwitz et al. teaches that the combination of both CTLA-4 blockade, which is mediated by contacting T cells in a mammalian host with an antibody that binds specifically to the extracellular domain of CTLA-4, and a vaccine consisting of GM-CSF- or IFN-γ-expressing tumor cells resulted in inhibition of tumor growth in the host; see entire document (e.g., the abstract). In contacting the T cells in the host with the GM-CSF- or IFN-γ-expressing tumor cells, the T cells are contacted with both a self antigen preparation, namely the tumor cell, and an immune response stimulating agent, namely GM-CSF or IFN-γ.

18. Claims 21, 23, 24, 27, and 31 are rejected under 35 U.S.C. § 102(a) as being anticipated by van Elsas et al. (*J. Exp. Med.* **190**: 355-366, 1999; of record).

van Elsas et al. teaches that the combination of both CTLA-4 blockade, which is mediated by contacting T cells in a mammalian host with an antibody that binds specifically to the extracellular domain of CTLA-4, and a vaccine consisting of GM-CSF-expressing tumor cells resulted in inhibition of tumor growth in the host; see entire document (e.g., the abstract). In contacting the T cells in the host with the GM-CSF-expressing tumor cells, the T cells are contacted with both a self antigen preparation, namely the tumor cell, and an immune response stimulating agent, namely GM-CSF. van Elsas et al. teaches mice surviving tumors after combination treatment developed

autoimmune-mediated depigmentation, an effect of autoreactive T cells; see, e.g., the abstract. van Elsas et al. teaches that recent work has shown that unaltered self antigens aberrantly expressed in tumors or expressed in tissue-specific fashion can be recognized by T cells isolated from mice or human patients, which suggests autoreactive T cells escape thymic deletion and reach the periphery, where they can in some instances be activated and involved in antitumor immune responses (page 355, column 1). van Elsas et al. teaches the blockade of CTLA4, which inhibits CTLA-4 signaling, prevents the induction of peripheral T cell tolerance upon vaccination with peptides under tolerogenic conditions (paragraph bridging pages 355 and 356). van Elsas et al. teaches their results and other's indicate that T cell tolerance against melanocyte self antigens can be broken to induce antitumor immunoreactivity (page 363, column 2; and page 364, column 1).

19. Claims 21, 23-25, 27, 28, and 31 are rejected under 35 U.S.C. § 102(e) as being anticipated by US Patent No. 6,051,227 A, as evidenced by Lavesque et al. (*J. Clin. Lab. Anal.* **9**: 123-128, 1995) and van Elsas et al. (*J. Exp. Med.* **190**: 355-366, 1999; of record).

As evidenced by Lavesque et al., both prostate tumor cells and the normal prostate cells from which the tumor cells arose express PSA (abstract).

As evidenced by van Elsas et al., contacting T cells in a mammalian host with the anti-CTLA-4 antibody of Leach et al. is capable of breaking immune tolerance to stimulate an autoreactive T cell immune response to normal cells and tumor cells expressing a common self antigen; see entire document, particularly the paragraph bridging pages 361 and 362 and page 364, column 1.

U.S. Patent No. 6,051,227 A ('227) teaches a method for inhibiting the growth of tumor cells in a mammalian host comprising contacting the T cells of the mammal with a combination of an antibody that binds specifically to the extracellular domain of CTLA-4

to inhibit CTLA-4 signaling and a self antigen preparation comprising a tissue-specific self antigen. '227 teaches the self antigen preparation can be a tumor vaccine containing the self antigen; and '227 teaches the tumor vaccine can comprise cytokine transduced tumor cells containing the self antigen (column 33, Example 9). '227 teaches the self antigen preparation can comprise tumor cell lysates containing the self antigen. '227 teaches the contacting step can occur ex vivo, such that the activated T cells can be administered to the host. '227 teaches that the T cells of the mammal can also be contacted with an immune stimulating agent, e.g., B-7, INF-g, and GM-CSF (see, e.g., column 33, Example 9). '227 teaches CTLA-4 blockade synergizes with GM-CSF, and probably other lymphokines, to result in complete tumor rejection (column 33, Example 9).

Claim Rejections - 35 USC § 103

20. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

21. Claims 21 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over van Elsas et al. (*J. Exp. Med.* **190**: 355-366, 1999; of record) in view of US Patent No. 6,051,227 A.

van Elsas et al. teaches that which is set forth above. In addition, van Elsas et al. teaches reinfusion of autologous tumor-infiltrating lymphocytes specifically recognizing particular self antigens (i.e., gp100 or tyrosinase) led to tumor regressions (page 363, column 2).

van Elsas et al. does not expressly teach contacting T cells of a mammalian host *ex vivo* with the combination of an immune response stimulating agent and CTLA-4 blocking agent and then administering the activated T cells to the host to inhibit the growth of tumor cells in the host.

US Patent No. 6,051,227 A ('227) teaches that which is set forth above.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to modify the method of van Elsas et al. by contacting T cells of a mammalian host *ex vivo* with the combination of an immune response stimulating agent and CTLA-4 blocking agent and then administering the activated T cells to the host to inhibit the growth of tumor cells in the host, because '227 teaches the *ex vivo* activation of autologous T cells can be transferred back into the mammal to inhibit the growth of tumor cells in the mammal. One ordinarily skilled in the art at the time of the invention would have been motivated to do so to treat tumors.

Double Patenting

22. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

23. Claims 21, 23-25, 27, 28, and 31 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-23 of U.S. Patent No. U.S. Patent No. 6,051,227 A. Although the conflicting claims are not

identical, they are not patentably distinct from each other because the instant and copending claims are drawn to nearly the same methods for inhibiting the growth of tumor cells in a mammal.

At Applicant's request (page 13, paragraph 4, of the amendment filed June 5, 2003), this issue will be held in abeyance until a determination of allowable subject matter is made in the instant application.

24. Claims 21, 23-25, 27, 28, and 31 are directed to an invention not patentably distinct from claims 1-23 of commonly assigned U.S. Patent No. 6,051,227 A. Specifically, although the conflicting claims are not identical, they are not patentably distinct from each other for the reasons set forth in the rejection above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned U.S. Patent No. 6,051,227 A, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 35 U.S.C. 103(c) and 37 CFR 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

25. Claims 21, 23, 25, 27, and 31 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U.S.

Patent No. 5,811,097 A. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant and copending claims are drawn to nearly the same methods for inhibiting the growth of tumor cells in a mammal.

At Applicant's request (page 13, paragraph 4, of the amendment filed June 5, 2003), this issue will be held in abeyance until a determination of allowable subject matter is made in the instant application.

26. Claims 21, 23, 25, 27, and 31 are directed to an invention not patentably distinct from claims 1-11 of commonly assigned U.S. Patent No. 5,811,097 A. Specifically, although the conflicting claims are not identical, they are not patentably distinct from each other for the reasons set forth in the rejection above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned U.S. Patent No. 5,811,097 A, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 35 U.S.C. 103(c) and 37 CFR 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

27. Claims 21 and 24 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U.S.

Patent No. 5,811,097 A in view of Heslop (*Baillieres Clinical Haematology* **7**: 135-151, 1994) for the reasons set forth in the previous Office action.

At Applicant's request (page 13, paragraph 4, of the amendment filed June 5, 2003), this issue will be held in abeyance until a determination of allowable subject matter is made in the instant application.

28. Claims 21 and 24 are directed to an invention not patentably distinct from claims 1-11 of commonly assigned U.S. Patent No. 5,811,097 A. Specifically, although the conflicting claims are not identical, they are not patentably distinct from each other for the reasons set forth in the rejection above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned U.S. Patent No. 5,811,097 A, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 35 U.S.C. 103(c) and 37 CFR 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

Conclusion

29. No claims are allowed.

30. The prior art made of record and not relied upon is considered pertinent to Applicants' disclosure. WO 97/20574 A1 teaches the combination of CTLA-4 blockade and tumor vaccines to inhibit the growth of tumor cells in a mammal. US 6,719,972 B1 teaches methods for inhibiting the growth of tumor cells in a mammal comprising administering an antibody that binds CTLA-4 to enhance T cell responses to a vaccinating material. US Patent No. 5,874,560 A teaches vaccinating materials to treat melanoma in a mammal. Gold et al. teaches adoptive transfer of ex vivo-activated T cells provides effective tumor-specific therapy of melanoma in mammals.

31. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
June 25, 2004

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